Project Report

# Summary

This report details an investigation into the production of risperidone microspheres using an automated platform to evaluate the effects of process parameters on particle size and distribution. Key variables included three continuous flow rates (15, 30, and 45 mL/min), two membrane sizes, and two manufacturing configurations: a fully automated system and a hybrid manual/automated setup.

Results indicate that the hybrid setup produced microspheres with significantly greater size consistency, achieving a standard deviation of approximately 12 µm compared to 21 µm for the fully automated process. Increasing the flow rate from 15 to 30 mL/min effectively reduced the mean droplet size, while a further increase to 45 mL/min yielded negligible changes. Membrane size did not significantly impact droplet size or dispersity.

Utilizing a hybrid manufacturing approach and higher flow rates are effective strategies for controlling microsphere size and reducing variability. Future work will focus on optimizing hardening times and other formulation parameters to control release rates.

# Introduction

The controlled release of active pharmaceutical ingredients is critical for optimizing therapeutic efficacy and patient compliance. Risperidone microspheres serve as a promising vehicle for sustained drug delivery, with particle size and size distribution as key determinants of the release profile. This study investigates the relationship between microsphere size, size blending, and resultant release rates, necessitating the establishment of a robust and reproducible manufacturing process.

An experimental investigation into the parameters governing risperidone microsphere formation was conducted using an automated platform. The study assessed the impact of key process variables on microsphere size and distribution, generating formulations at three continuous flow rates (15, 30, and 45 mL/min) and utilizing two membrane sizes (10x200 and 20x200) for size control.

To evaluate the manufacturing methodology, experiments were performed using two configurations: a fully automated "autobuild" system and a "hybrid" setup employing manual pumps for formulation, followed by automated tangential flow filtration (TFF) for washing. Additionally, an experiment explored the effects of process timing by varying hardening time (6, 12, and 18 minutes) prior to TFF recirculation.

# Objectives

1. Compare consistency of automated and hybrid manufacturing platforms.

2. Assess the impact of flow rate and membrane size on particle characteristics.

3. Evaluate the effect of hardening time on particle formation.

# Methodology

## Investigation of Process Parameters on Microsphere Size

Risperidone microspheres were fabricated to evaluate the effects of manufacturing process parameters on particle size and distribution. Formulations were prepared in triplicate to increase yield. Two distinct manufacturing configurations were tested: a fully automated platform and a hybrid setup. The hybrid process utilized manual axial-flow filtration (AXF) pumps for droplet formation, followed by an automated tangential flow filtration (TFF) system for washing. Within each setup, two variables were systematically altered: continuous phase flow rates of 15, 30, and 45 mL/min, and two membrane sizes (10x200 and 20x200) to assess their impact on microsphere formation. The resulting droplet size and size distribution were characterized for each experimental condition.

## Evaluation of Hardening Time

The effect of hardening time on microsphere properties was determined using a standardized formulation prepared in triplicate on the fully automated platform. The hardening time, defined as the interval between the addition of the formulation to the collection beaker and the initiation of TFF recirculation, was varied at three time points: 6, 12, and 18 minutes.

# Results

The hybrid platform produced more uniform particles (droplet SD ≈ 12 µm) compared to the automated system (SD ≈ 21 µm). Increasing the flow rate to 30 mL/min reduced both particle size and variability; further increases had a negligible effect. Membrane size did not significantly influence results, and findings related to hardening time were inconclusive.

# Conclusion

This investigation demonstrated that risperidone microsphere characteristics can be controlled through the modulation of key process parameters. The continuous phase flow rate significantly influenced particle size; increasing the flow rate decreased the average and median droplet sizes post-AXF. A hybrid manufacturing setup using manual AXF pumps followed by automated TFF washing resulted in formulations with superior consistency and a lower standard deviation in droplet size distribution (~12 µm) compared to the fully automated platform (~21 µm). Decreasing the membrane size from 20x200 to 10x200 did not meaningfully reduce droplet size or improve the dispersity of the microsphere population. These results indicate that flow rate and process configuration are primary drivers for tuning microsphere size, while membrane size has a lesser impact under the tested conditions.